REMARKS

This amendment is submitted in an earnest effort to bring this application to issue without delay.

Applicants wish to reiterate their claim to the benefit of their Hungarian priority application P0303313 filed 9 October 2003 pursuant to the International Convention. A certified copy of the Hungarian patent application has been filed in PCT/HU 2004/000092 filed 6 October 2004 of which the instant application is the US National Phase. The Examiner has already acknowledged Applicants' perfected right of priority.

Applicants have canceled claims 1 through 70 and are submitting new claims 71 through 100. Antecedent basis for new claims 71 through 100 may be found in the specification on pages 15 through 34 and in the specific examples. Thus claims 71 through 100 are now in this application and are presented for examination.

Applicants had elected as the elected species containing estrogen and progestin as the pharmaceutically active ingredients according to new claim 80. Applicants made the election of species in response to a telephone call from the Examiner. All of claims 71 through 86 now presented are readable on the elected species of claim 80.

None of the claims now presented is a multiply dependent claim and so the objections to the claims last presented on the grounds of improper multiple dependency are no longer relevant.

New independent claims 71 and 80 recite clear and definite numerical ranges for all ingredients, including the polyoxyethylene-glyceryl-trioleate, propylene glycol, isopropyl myristate and the hyaluronic acid salt and Applicants believe that no claim now presented is indefinite and so all claims now presented comply with the requirements of 35b USC 112, second paragraph.

The Examiner has rejected claim 17 and all other claims readable on the elected species last presented as obvious under 35 USC 103 citing the combination of EP 0509 761 B1, in combination with US Patent Appl. 2004/0192620 to BUNSCHOTEN et al, in further view of US Patent 5,326,566 to PARAB, the MENOPAUSE article of BRYNHILDSEN, and in further view of POUYANI et al. The Examiner believes that EP 0509 761 B1 alone is a very close reference to the presently claimed invention since the reference discloses a lyotropic liquid crystalline arrangement containing a pharmaceutically active ingredient as well as propylene glycol, polyoxyethylene glycol trioleate, and even hyaluronic acid. The Examiner believes that the secondary references disclose or suggest everything else that is present in the instantly claimed invention and so it would be obvious to combine EP 0509 761 B1 with the secondary references to arrive at the presently claimed invention.

Applicants do not agree with the Examiner's analysis of EP 0509 761 B1 and do not agree with her analysis of some of the secondary references either. One of the first differences that

Applicants notice between the lyotropic liquid crystalline arrangement disclosed in EP 0509 761 B1 and the presently claimed liquid crystal gel is that the reference composition is disclosed as an anhydrous transdermal composition. See page 2, lines 3 and 37 of the reference. According to the present invention, the compositions contain an oil phase (non-aqueous phase) containing isopropyl myristate and an aqueous phase containing water, ethanol, benzyl alcohol and either sodium hyaluronate or the zinc complex of hyaluronic acid. See page 21, lines 13 to 26. Thus the anhydrous lyotropic liquid crystalline arrangement disclosed in the reference is not equivalent to the instantly claimed invention having both an oil phase and an aqueous phase.

There are other differences too. Applicants' presently claimed invention in the aqueous phase contains benzyl alcohol, ethanol, water and either the zinc or sodium hyaluronate. The Examiner agrees that these ingredients are not part of the invention disclosed in EP 0509 761 B1, but believes that the reference discloses the addition of hyaluronic acid to the lyotropic liquid crystalline arrangement. No where do Applicants see any specific mention of hyaluronic acid as an ingredient in the reference composition. Applicants do see mention of a polymer, the a value of which is > 0.6, but the only specific polymer disclosed within that definition is polyoxyethylene 35,000. See the bottom of page 2 of the reference. Such a polymer is far removed structurally from hyaluronic acid. Thus Applicants do not agree

that the reference either discloses hyaluronic acid in the lyotropic liquid crystalline arrangement or suggests same.

Furthermore Applicants do not employ hyaluronic ic acid. Applicants employ aqueous salts or complexes of hyaluronic acid, which are soluble in Applicants' aqueous phase that is not a part of the lyotropic liquid crystalline arrangement disclosed in the reference. The reference compositions require that liquid polyethylene glycol and solid polyethylene glycol be included and these ingredients are not found in Applicants' presently claimed composition. Applicants employ instead of the PEGs, isopropyl myristate as a penetrant or as the solvent for the oil phase of the liquid crystal gel.

Another consideration is that Applicants' active ingredients in the elected species composition include an estrogen and a progestin used together in hormone replacement therapy. The active ingredient in the reference is deprenyl, an MAO inhibitor.

Among the secondary references BUNSCHOTEN et al discloses compositions that may be in gel form and administered transdermally or transmucosally that include the HRT such as an estrogen and a progestin. See paragraphs 0091 and 0092 of the reference. Paragraph 0092 mentions hyaluronic acid apparently as an auxiliary agent in the transmucosally administered compositions. Applicants see no mention, however, of a liquid crystalline gel, no mention of such an arrangement with both an aqueous portion and an oil portion, no mention of the sodium hyaluronate or zinc complex of

hyaluronic acid. Nor do Applicants see any mention of the surfactant polyoxyethylene glycol trioleate or the particular 2:1 ratio of that compound to propylene glycol as the co-surfactants. Thus there is still no teaching from the combination of EP 0509 761 B1 and BUNSCHOTEN et al to prepare a liquid crystalline gel for the transdermal administration of any pharmaceutically active ingredient, including an estrogen/progestin combination, containing sodium hyaluronate or zinc hyaluronic acid in an aqueous portion thereof, and an oily portion thereof as well. Applicants point out that the presently claimed compositions are administered transdermally, that is through the skin, and not transmucosally, that is through a mucous membrane.

The Examiner has cited the PARAB reference apparently for its disclosure that isopropyl myristate is a well-known penetrant enhancer for topical preparations. See col. 3, line 15 of the reference. There is no disclosure, however, of using this compound as the solvent for the oily phase in a liquid crystalline gel according to the present invention containing both an aqueous phase and an oily phase. Nor is there any suggestion to include hyaluronic acid sodium salt or the zinc complex of hyaluronic acid to the composition.

The BRYNHILDSEN et al reference discloses transdermal compositions containing an estrogen and a progestin for HRT administered using a transdermal patch. According to the present invention Applicants do not use a transdermal patch, but instead

use a liquid crystalline gel containing the active ingredients. Applicants avoid the transdermal patch because use of such a patch promotes irritation and use instead the liquid crystalline gel to avoid this problem. See page 44, lines 11 through 18 of the present application.

The Examiner has cited POUYANI et al for its alleged disclosure that hyaluronic acid would be an excellent drug carrier for any pharmaceutical, including transdermally administered pharmaceuticals. Once again Applicants do not use hyaluronic acid, but instead use sodium hyaluronate or zinc hyaluronic acid complex, the latter two compounds having a greater water solubility, and therefore provide the Applicants with an important component of the aqueous phase of their compositions. However, POUYANI et al does not disclose that hyaluronic acid per se would be a great drug carrier. In fact the reference discloses in col. 1, lines 47 to 61, and col. 2, lines 48 to 60, that hyaluronic acid lacks stability and is easily degraded and so would be expected to be a poor drug carrier unless the hyaluronic acid is significantly structurally modified, that is chemically stabilized, by reaction of the hyaluronic acid with a dihydrazide to form a functionalized hyaluronic acid with a dihydrazido functional group according to Scheme I in col. 4 of the reference.

In the presently claimed invention Applicants do not use hyaluronic acid functionalized with a dihydrazido group, but use sodium hyaluronate or zinc hyaluronic acid, which are structurally

far removed from the functionalized hyaluronic acid disclosed in the reference.

In view of the above, Applicants have a good argument that the elected species claims, which are now claims 80 to 85 are patentably distinguishable over the cited combination of references. Furthermore because the Examiner has not found a sufficient basis to reject claims 80 to 85 as obvious under 35 USC 103 in view of the cited prior art, she is asked expand her search to cover the liquid crystalline gel containing any pharmaceutically active ingredient, not just the ingredients for HRT and examine claims 86 through 100. Furthermore the Examiner should even consider the patentability of the liquid crystalline gel of claims 71 through 84 which are directed to the liquid crystalline as a drug carrier without any pharmaceutically active ingredient at all. Note that claims 71 through 79 and 86 are considered readable on the elected species of claim 80.

Applicants now give the following direct comments regarding the Examiner's rejection of the claims last presented under 35 USC 103 and reasons why such a rejection should not be maintained against any claim now presented.

Our application is new. Equivalent patents already have been granted following examination in Europe, Eurasia, and in Hungary without any problem. The US Examiner strongly misunderstands our aim with the invention. We enclose documents all

showing that our invention was accepted without any novelty problem after examination in Europe, Eurasia, and in Hungary.

The essence of our invention is a special liquid crystal gel containing four components: polyoxyethylene-glyceryl-trioleate, propylene-glycol, isopropyl myristate and a hyaluronic acid salt or complex. Our invention is not a patch at all. We do not mention the word "patch" in the invention, only in the technical art.

We do not agree with the Examiner's opinion that the present invention is obvious in view of the cited prior art, because the special technical feature of our invention is not only hyaluronic acid (actually the Na salt or Zn complex thereof), and not polyoxyethylene-glyceryl-trioleate, but the four components (polyoxyethylene-glyceryl-trioleate, propylene-glycol, isopropyl myristate and a hyaluronic acid salt or complex) together, in a given ratio as a transdermally administered liquid crystal gel. The four components are coequal, the order between them is only at random.

Another main misunderstanding is that our invention relates to a liquid crystal gel and not to a patch, at all. The "liquid crystal" is a physicochemical term for the consistence of the materials. The "patch" ("plaster") is an adhesive sheet containing active drug, while our invention is a gel itself, a special liquid crystal gel.

Our analysis of the specifically applied prior art references is as follows:

EP 509761 (Stab et al.):

The claim of patent EP 509761 is composed of an anhydrous lyotropic liquid crystalline arrangement with given components, in a given ratio:

"1-30 w. % Deprenyl (active agent), 40-70 w. % liquid polyoxyethylene, 10-20 w. % solid polyoxyethylene, 2-30 w. % nonionic surface active agent, 2-20 w. % propyleneglycol, if desired 0.5-2 w. % polymer ... as emulsifying agent".

It does not relate to a liquid crystalline system that would contain one named ingredient in general - for example — polyoxyethylene or propylene glycol.

The polyoxyethyleneglycol compounds used by EP 509761 and the polyoxyethyleneglyceryl-trioleate compound used in our invention are different compounds. The examples of the reference use different PEG compounds and not polyoxyethylene-glyceryl-trioleate.

According to EP 509761 for the liquid crystalline arrangement it is necessary to have two different polyoxyethyleneglycol compounds (liquid and solid) together. Our invention relates only to one PEG compound, polyoxyethylene-glyceryl-trioleate. Our invention does not use any solid ingredients.

Hyaluronic acid is not mentioned in EP 509761, only "polymer" in the claim 1, "polysaccharide" in the description, and in the

composition examples only xanthan gum is named. Our invention does not use hyaluronic acid but hyaluronic acid salt or complex. There are many kinds of polymers, many kinds of polysaccharides. For one "skilled in the art" it is not evident to think from "polymer" or from "polysaccharide" directly to hyaluronic acid. Hyaluronic acid (a special polysaccharide, available in the human body) and xanthan gum are two so different polysaccharide structures that for an expert it is not evident to see in the reference the "xanthan gum", and think of "hyaluronic acid".

Our invention relates to a liquid crystal gel containing four main components: polyoxyethylene-glyceryl-trioleate, propylene-glycol, isopropyl myristate and a hyaluronic acid salt or complex, in a given ratio. Beyond these ratios the liquid crystal gel does not exist. These ratios are not the same as in case of the reference.

According to EP 509761 the liquid crystalline arrangement is anhydrous. Our invention relates to a liquid crystal gel containing water too. This difference has not just technologically but also pharmaceutically significance, because the skin (our biggest organ) is less permeable for adipic, anhydrous active agents, than for aqueous systems. Or even between the lipophilic agents which have serious skin irritability effects because following application to the skin, they remain longer on the skin or in the skin, and they must take a lot more time to wash out, than in the aqueous systems, such as the presently claimed

compositions. Consequently, an anhydrous delivery system can not be equivalent to an aqueous delivery system. Applicants note that in all of the claims now presented water is actually a part of the compositions.

Another further difference between EP 509761 and our invention is, that our gel system never comprises active agents in solid, crystal condition, as in case of deprenyl.
Our aim was to find an aqueous gel system, which produces a more comfortable feeling and it can dissolve universally the polar and apolar active agents, too. The advantage of our transdermal liquid crystal gel is that the weakly water soluble steroids can also release from the gel very well.

US 2003/0192620 (Burschoten et al.):

The application related to a contraceptive method of administering newly synthesized estrogens and some progestin components in combination. In our invention we also use these progestins. The reference compositions may be in gel form. The mode of administration may be transdermal or transmucosal, too.

The expression "HRT" exists indeed in this reference. HRT means Hormone Replacement Therapy. But in this particular medical practice, this contraceptive indication mentioned by the reference is not a classic HRT indication. Contraception is used at woman below 40-45 years, while the classic HRT is used in menopause or

after menopause at woman over 40-45 years, against the symptoms coming in the menopause: osteoporosis, hot flush, and others. In the transmucosal delivery system of the reference it is recommended a usage of e.g. propylene glycol, fatty acid esters, hyaluronic acid; while transdermal delivery system administration is recommended only with the usage of e.g. fatty acid esters. Our invention is a transdermal and not a transmucosal gel. The reference does not mention any discrete composition or closed ratio between the recommended ingredients, although it would be the basis to find a new gel.

Isopropyl myristate is mentioned in the reference among 20 other penetration enhancing agents. It is very hard to believe that for an expert it is evident to pick up just isopropyl myristate from them, in the optimal ratio.

There is no teaching from the combination of EP 509761 and US 2003/0192620 to prepare our special liquid crystal gel.

US 5326566 (Parab et A):

The patent related to a topical composition for enhancing skin penetration of an active agent comprising dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate. The main essence of the patent is the usage of the dibutyl adipate, it does not recommend to use isopropyl myristate alone. And our liquid crystal gel does not comprise dibutyl adipate.

There is still no teaching from the combination of EP 509761, US 2003/0192620 and US 5326566 to prepare our special liquid crystal gel as covered in the claims now presented.

US 5616568 (Pouvani et A):

This patent relates only to functionalized (cross-linked) hyaluronate with dihydrazide. These compounds are totally different in terms of structure from our hyaluronates. Hyaluronic acid (a natural polysaccharide, available in the human body) consists of glucose-amine and glucuronic acid monomers, while the polymer in the mentioned reference is a semisynthetic compound, from the synthesis of hyaluronic acid with dihydrazide, resulting in the so-called "cross-linked" hyaluronates. We never mentioned in our invention the use of this special group of cross-linked hyaluronates. Thus the reference is not relevant to the presently claimed invention.

Menopausa abstract, 2002 (Brynhildsen et al.):
Our invention relates to a liquid crystal gel and not to a transdermal patch. The reference is therefore not relevant at all to the presently claimed invention.

Summarizing, to find a stable liquid crystal gel system, it is not easy. It needs an intense expertise, and many hours of experimental work. It is not enough to know just the information from the mentioned patents to make a new liquid crystal gel. We

have examined several unrelated branches of the pharmaceutical arts and have determined both what specific components and the concentration range required for each specific component to form a transdermal liquid crystal gel for a pharmaceutical composition that is chemically stable, homogeneous and non-greasy, while avoiding skin irritation and providing reliable transdermal absorption of the active ingredient into the bloodstream. Such a composition was not obvious from the prior art.

Applicants are enclosing a copy of a search report performed by the Hungarian patent Office in the corresponding Hungarian National Application. The Hungarian Patent Office found two references and designated each of these references a Category "A" reference indicating that the references are relevant merely to show the state of the art. Those references include Hungarian Patent 208 069 (equivalent to US Patent 5,523,093) and Hungarian Patent 211 953 (equivalent to US Patents 5,985,850 and 6,069,135). Applicants are submitting all of this information on PTO 1449 as well.

Applicants also note that the Hungarian Patent Office has granted a patent in the corresponding Hungarian Patent Application, the European Patent Office has granted a patent in the corresponding European Patent Application and the Eurasian Patent office has granted a patent in the corresponding Eurasian Patent Application.

Applicants would like to arrange a telephone interview with the Examiner to discuss the claims as now presented and the cited prior art, once the Examiner has had a chance to consider the new claims and the supporting arguments.

Applicants believe that all claims now presented are allowable and a response to that effect is earnestly solicited.

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Enclosures: PTO-1449
Hungarian Search Report Cover Pages from equivalent Foreign patents to present Application:
EP 1 673 063B1
Eurasian Patent 009900
E 003054 (Hungarian Patent)